With the Authors' Compts.

A CLINICAL AND EXPERIMENTAL INVESTIGATION INTO THE LYMPHOGENOUS ORIGIN OF TOXIC INFECTION OF THE CENTRAL NERVOUS SYSTEM.

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In a previous paper (1) we described the lesions in the posterior columns of the spinal cord in general paralysis, and pointed out their similarity with those in early tabes dorsalis. Our conclusion with regard to the starting-point of the degeneration was that it commenced in the intramedullary portion of the sensory fibres immediately the neurilemma sheath was lost. It is important to clearly differentiate this point from that at which the posterior roots undergo a constriction on passing into the cord, as they do not coincide; in fact in the region most usually concerned in tabes (lumbo-sacral) the neurilemma leaves the fibres at a point situated outside the constriction (2). Nevertheless we would speak of the nerves as intramedullary as soon as they lose Schwann's sheath.

During these observations on the sensory fibres, in which it was apparent that the absence of neurilemma played an important part in the localisation of the onset of the lesion, we naturally inquired into the condition of the intramedullary portion of the motor nerves, but found the changes in these as a rule difficult to trace. We therefore extended our investigations to the cranial nerves, and found that the lesions began in both sensory and motor roots at a point which corresponds to that already indicated in the spinal nerves; and the changes found therein form the first part of this paper.

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[1] Towards this research the British Medical Association has assisted by a grant of money.

While our attention was still confined to the posterior columns of the cord we had indications of the advisability of inquiring into what was already known of their lymphatic system, and we obtained evidence of a continuous flow of lymph upwards along the nerves, and that the main current lay at the periphery of the nerve bundles immediately under the fibrous sheath. References to the authors holding this view have been given in our previous publications, so that here a short recapitulation will suffice. It is well known that tetanus and rabies spread to the cord by the nerves; and in this connection we might mention the experiments of Marie and Morax (3) who, after cutting the nerve to the fore limb of an animal and later injecting a lethal dose of the tetanus toxin into the paw, found that no convulsions followed. Homén and Laitinen (4), after injection of streptococci into the sciatic nerve, traced the organisms upwards into the meninges of the cord; while Pirrone (5), experimenting with the pneumococcus, found changes in the cord, but limited to the side corresponding to the nerve injected. In addition to organisms, chemical and inert substances have been used with like results, *e.g.* Guillain (6) injected ferric chloride into the sciatic nerve, subsequently introducing potassium ferrocyanide into the general circulation, and found Prussian blue in the posterior roots. Sicard and Bauer (7), using China ink, observed, after injection into the nerve, that the granules ascended along it towards the cord. It was presumable therefore that, if these views were correct, we ought to find in the cord of cases in which some septic focus existed, lesions of the posterior columns caused by toxins ascending in the lymph stream. On examining cases of brachial neuritis (infective), bed sores, suppurating knee-joint, septic psoas abscess, we found, in the cord of all, the lesions expected. These also commenced at the vulnerable point above indicated, and resembled in their distribution early tabetic degenerations (8).

Bearing these facts in mind, the question of a possible lymphogenous infection of the central nervous system seemed worthy of further investigation, owing to the apparent facility with which toxins gained access by the nerves; and it was with a view to testing this that our experiments were conducted. Besides, apart from the question of etiology, the introduction of toxins by the nerve lymph paths promised, if successful, to offer a convenient means of inducing cord and cranial nerve lesions, and to afford one the opportunity of studying them in their early phases. We have already published a series of clinical cases (1 and 8) showing the lesions found in the spinal cord in general paralysis and in other toxic conditions, and before giving the results of our experiments we submit the following cases illustrative of lesions of the cranial nerves.

Lesions of Cranial Nerves in Toxic Conditions.

Clinical Cases.

Case 1.—An ataxic general paralytic. The first symptoms were noticed about three years before his death.

Examination of the pons and medulla showed the following lesions of the *cranial nerves*:—

Third Nerve.—Both third nerves were affected to a slight degree. By the Marchi method the degeneration was exhibited in the form of small, round, black globules, which could be followed along the nerve fibres from the periphery almost to the nucleus of origin.

Fourth Nerve.—The left fourth nerve was affected much more than the right. In the latter, globules were present, as in the third nerve, but were larger. In the left nerve the degeneration was in the form of larger and more irregular masses, which were arranged in series along the nerve fibres. They could be traced from the point where the fibres lost their neurilemma sheath—and the lesion was most intense in this region—to the nucleus of origin. There was no degeneration in the fibres outside the pons.

Fifth Nerve.—The left fifth nerve showed more degeneration than any other cranial nerve, and exhibited many interesting changes; the right was also affected, but to a less degree. Immediately beyond the point where the fibres had lost their neurilemma sheath (Photo 4), an intense lesion was found, which by a low power seemed to consist of large irregular masses arranged in rows. But with a higher power the changes were seen to be of different types. In some fibres there were series of large irregular masses similar to those which are characteristic of Wallerian degeneration; in other fibres the reaction assumed the form of black sinuous threads (see Photos 1 and 3); in some, round or oval globules of various sizes were seen, and some fibres showed no Marchi reaction at all.

These various types of degeneration indicate different degrees of injury to the fibres. We are thus able to explain the fact that the degeneration was continued along many of the fibres of the descending fifth root, even as far as the first cervical segment (Photo 6). In the case of these fibres there must have been a necrosis of the axis-cylinder, as well as of the myelin sheath, immediately inside the point where the fibres lost their neurilemma sheath, which would produce a Wallerian degeneration in the portion of the fibres beyond the point of injury. In the descending root, however, there were many fibres which showed no degeneration, and these would correspond to the unaffected fibres, which were seen in the first part of the intracranial portion of the fifth nerve, and also to those fibres which exhibited the slighter degrees of change.

In the right fifth nerve round and oval globules were present, but there was no evidence of any necrosis such as was met with in the left nerve. Corresponding to this there was an absence of degeneration amongst the fibres of the right descending root.

Sixth Nerve.—In both sixth nerves there was considerable degeneration demonstrated by the Marchi method. Here the thread-like form was more in evidence, accompanied by many round and oval globules.

Seventh and Eighth Nerves.—In these nerves very little degeneration was found.

Ninth and Tenth Nerves.—On the left side there were many affected fibres in which the degeneration could be traced from near the periphery of the medulla oblongata to the fasciculus solitarius. In the right nerves there was little change.

Eleventh Nerve.—The right nerve in this case showed a marked lesion, which could be followed from the periphery to its nucleus.

Twelfth Nerve.—There was practically no lesion of the fibres of the twelfth nerves.

In this case it was evident, from the appearances found, that an acute degenerative process had supervened on a chronic morbid condition. In the ninth and tenth nerves especially there was evidence that a slow atrophy had taken place, particularly near the border of the medulla oblongata. But in the left fifth nerve, and to a less extent in the left fourth and both sixth nerves, the increase in the amount of the Marchi reaction and the presence of the large, irregular masses, and the fact that the degeneration in the fifth could be followed from the edge of the pons along the fibres of the descending root of the nerve to the first cervical segment, indicated an acute degenerative process.

Case 2.—Melancholia. At the post-mortem examination a tumour was found in the anterior part of the left lobe of the cerebellum; there was also an acute basal meningitis, which was more marked on the left side of the pons and medulla. In this case the third nerves were not examined.

Fourth Nerve.—Both fourth nerves showed some degeneration which could be followed from the point where the fibres pierced the pia mater to the nucleus of origin. Most of the Marchi reaction was seen in the form of round or oval droplets, but the thread-like type was frequently present.

Fifth Nerve.—The maximum intensity of the meningitic process was at the level of the left middle cerebellar peduncle, and the cranial nerves which were nearest to this region showed most degeneration.

The fifth nerves were both affected, but in the left nerve most of the fibres showed an acute degenerative reaction. This was seen chiefly in the form of round or oval globules of various sizes ; but with this there was also some thread-like degeneration, and in some fibres the affected myelin lay in larger and more irregular masses.

Some degeneration could be traced to the motor nucleus.

In this case, however, although there was such an intense degeneration in the fibres of the left nerve, only a small number of affected fibres were present in the descending fifth root.

Sixth Nerve.—Some Marchi reaction, in the form of round globules, was present in both sixth nerves.

Seventh and Eighth Nerves.—The seventh and eighth nerves on the left side showed considerable degeneration, but the right nerves were affected to only a slight degree.

On the left side the degeneration could be followed from the periphery of the pons to the nucleus in both nerves. In the seventh nerve there was some thread-like degeneration, associated near the periphery with some larger irregular masses ; but in the other parts of this nerve and in the eighth the reaction consisted chiefly of round or oval globules of various sizes.

Ninth, Tenth, and Twelfth Nerves.—In all these nerves, globules of Marchi reaction were present. In the left tenth nerve the degeneration could be traced from the periphery around the fasciculus solitarius to the nucleus ambiguus.

In this case the most important fact to be observed is that the degree of the lesion varied with the intensity of the meningitic process. This was most marked at the level of the middle cerebellar peduncle, especially on the left side, and it was in this region that the cranial nerves were most affected ; in fact, those connected with the lower portion of the medulla, where the meningitic changes were scanty, exhibited only a slight degree of degeneration. The lesion of the left fifth nerve was very acute, as shown by the character of the Marchi reaction, but there were few degenerated fibres in the descending fifth root ; there can be little doubt, however, that if the process had lasted a little longer, necrosis of the axis-cylinders and myelin sheath would have been produced, and there would have followed a Wallerian degeneration of the fibres extending throughout the descending root.

At the same time it is interesting to find that the lesions in the fibres began at the same point, viz. immediately they had lost their neurilemma sheath, and that they were of the same character, as in cases where the septic focus was extra-cranial (see *infra*).

Case 3.—General paralysis. Gait markedly ataxic.

Cranial Nerves.—Third and Fourth Nerves.—Some degeneration present in the form of round droplets.

Fifth Nerve.—Both fifth nerves affected to a considerable extent. Descending root nil.

Sixth Nerve.—Considerable degeneration.

Seventh and Eighth Nerves.—Slight degeneration.

Tenth and Twelfth Nerves.—Very slight degeneration. There was considerable degeneration in both superior cerebellar peduncles.

Case 4.—Melancholia. Cause of death—General tuberculosis. Suppuration of the mastoid cells on both sides.

Cranial Nerves.—Third Nerve.—Some degeneration.

Fourth Nerve.—Considerable degeneration.

Fifth, Sixth, Seventh, and Eighth Nerves.—Much degeneration in all these nerves on both sides. Threadlike, round, and large irregular types present.

Case 5.—General paralysis.

Cranial Nerves.—Third and Fourth Nerves.—Very little degeneration.

Fifth Nerve.—Only one fifth nerve showed much degeneration.

Sixth Nerve.—Maximum degeneration. Both nerves affected.

Seventh Nerve.—Considerable degeneration on both sides.

Eighth, Ninth, and Tenth Nerves.—Little degeneration.

Twelfth Nerve.—Some degeneration on both sides.

Case 6.—General paralysis.

Cranial Nerves.—Third and Fourth Nerves.—Slight degeneration.

Fifth Nerve.—Considerable degeneration of the peripheral type, *i.e.* the degeneration was found only in the peripheral portion of the myelin sheath, the rest of the fibre showed no change.

Sixth and Seventh Nerves.—Considerable degeneration in the form of round globules.

Eighth Nerve.—Some degeneration of the peripheral type.

Tenth and Twelfth Nerves.—Very little degeneration.

Case 7.—General paralysis.

Third and Fourth Nerves.—Practically no degeneration.

Fifth and Sixth Nerves.—Considerable degeneration on both sides.

Seventh and Eighth Nerves.—Slight degeneration.

Ninth, Tenth, and Twelfth Nerves.—Practically no degeneration.

Case 8.—General paralysis.

Necrosis of skin over the right shoulder, muscles bare, pus burrowing amongst muscles, abscesses in the right trapezius. Very little degeneration in any cranial nerve excepting the eleventh on the right side.

Case 9.—General paralysis.

Some changes in the *sixth, seventh, and eighth cranial nerves.* Practically nil in the others.

Case 10.—General paralysis.

There was an acute degeneration in *one fifth nerve.* Practically nil in the other cranial nerves.

In this series of ten cases in which the cranial nerves were examined there are a few points to which we wish to draw attention.

The series included eight cases of general paralysis, one of tumour of the left lobe of the cerebellum in which an acute basal meningitis was the ultimate cause of death, and one case of general tuberculosis. In the last-mentioned and in one general paralytic a septic process was present during life which seemed to have a direct causal relation with the lesion found in the cranial nerves. In the case dying of general tuberculosis this consisted of chronic middle ear and mastoid disease, and the maximum lesion was found in the seventh and eighth nerves, although there was considerable change in the sixth, fifth, and fourth nerves. In the general paralytic there was necrosis of the skin over the right shoulder, with abscesses in the deep muscles of the neck, and especially in the trapezius. The right eleventh nerve showed considerable degeneration, but in the others there was little to be found.

In the remaining cases, in which no septic focus was found, the nerves connected with the pons, fifth, sixth, seventh, and eighth were more frequently and more seriously affected than those connected with the medulla oblongata. Again, the lesion commenced where the fibres lost their neurilemma sheath, and was of precisely the same character in motor and sensory nerves, and in no nerve was there any recognisable change in its extra-pontine portion.

The next point to be considered is the character of the lesion, as exhibited by the Marchi method. All degrees of degeneration were seen. The most intense was that in which there had been a necrosis of the axis-cylinder and of the myelin sheath in the left fifth nerve of Case 1, with consequent Wallerian degeneration, which could be followed in the descending fifth root to the first cervical segment of the spinal cord.

The other forms in which the degeneration was seen were (*a*) the slender moniliform thread, (*b*) the peripheral type in which the portion of the myelin sheath farthest from the axis-cylinder was affected and the remainder of the fibre showed no change, and (*c*) the type which consisted of small, scattered, round or oval globules. As to the significance of these various types it is impossible at present to speak with certainty, but in all probability they depend upon the intensity of the degenerative process. It should be mentioned that even in the most acute cases, side by side with the fibres showing signs of intense lesion, lay others in which no sign of degeneration was demonstrated by the Marchi method.

The last point to be mentioned is, that in several of the chronic cases the evidences of degeneration were most marked at a little distance inwards from the periphery of the pons or medulla.

This condition is present to a certain extent in most chronic cases, and was well seen in the tenth nerve of Case 1, who was a general paralytic of three years' standing. Further examination of this condition, by Medea's modification of Mann's method (9), demonstrated that although the axis-cylinders could be traced from the point where they pierced the pia mater, no myelin was present around them for some distance inwards. Evidently in these chronic cases a slow atrophy of the myelin takes place in the portion of the fibres most exposed to the attack of some weak toxin which approaches along the perineural sheath of the nerve. This may proceed until the axis-cylinder is laid bare, and therefore, as all the myelin in this peripheral portion of the fibre has disappeared, there is nothing left to give a Marchi reaction.

Toxic Lesions of the Spinal Cord and Cranial Nerves produced Experimentally.

At the suggestion of Professor Lorrain Smith, in whose laboratory the experiments have been conducted, we adopted the following method. Celloidin capsules were filled with a broth culture of a certain organism, then sealed and laid along-side the exposed sciatic nerve, after which the gluteal muscles were stitched in place and the wound closed. As toxins are known to diffuse through the wall of these capsules, we assumed that they would find their way into the ascending lymph stream of the nerves and so to the cord, where their presence would be demonstrated by the ensuing degeneration. The organisms we first employed were staphylococcus pyogenes aureus, bacillus pyocyaneus, Gaertner's bacillus, and the bacillus coli; later we used the organisms taken from cases of acute colitis. We commenced our experiments at the beginning of 1905 and at first used organisms whose virulence had not been raised in any way. We found, however, that in order to obtain definite lesions it was necessary to do so, and further, that it was advantageous to renew the capsule from time to time in order to maintain the supply of toxin. We purposely ignored at this stage the question of the predilection of certain organisms for the nervous system, and kept strictly to our original intention of confirming our own views and those of others on the direction of the lymph stream in the spinal roots, and the possibility of cord infection by this channel.

Five successful experiments have been examined by the Marchi method; three on the cord and two on the pons and medulla. In the latter the capsule with its bacteria was implanted under the skin of the cheek, and the result of these two experiments has been to demonstrate certain special changes which occur in the intramedullary portion of nerves, especially motor nerves, in toxic conditions. The pons and medulla were cut in serial section in their entirety, and we eliminated as far as is possible the artefacts of injury incidental to the autopsy, by merely removing the bony covering and hardening *in situ* for one week in formalin 10%. Later the tissue was immersed in 2% potassium bichromate before treatment with the Marchi method. Control experiments with capsules containing sterile broth were also performed. These yielded negative results.

In the following description it has been necessary to go into detail, especially with regard to the cranial nerves, as in each of these the degeneration varied in intensity as well as in type, for reasons at present difficult to understand.

Rabbit 1.—Capsule under Skin of Cheek.—Third Nerve.—This nerve was degenerated in its entire intramedullary course from its point of emergence back to the nucleus of origin, towards which, however, the changes were less marked. The myelin sheath showed as long, thin, black threads, with moniliform swellings at intervals, marking out the path of the nerve in parallel or sinuous lines (Photo 1).

Fourth Nerve.—The degeneration here was much less than in the third nerve. There were sinuous filaments of altered myelin, but these were short, and situated only at the point of emergence. The degeneration rapidly decreased from below upwards, and at the nucleus of origin there was no appreciable change.

Fifth Nerve.—There was a high degree of alteration in both sensory and motor portions. In the latter, the degeneration took the form of short, thin, black filaments with moniliform swellings mixed with swollen globules which could be traced into the main nucleus of origin, and for a short distance upwards along the mesencephalic root.

In the former, the degeneration was of the same type but greater in degree, and extended in the descending root as far as the level of the seventh nucleus.

Sixth Nerve.—There was a higher degree of degeneration in this nerve than in any other, and the morbid appearances were similar to those of the third nerve, but somewhat more advanced. The maximum of degeneration was found in the anterior third of the nerve between a point just posterior to the corpus trapezoides and the margin of the pons. In this portion the myelin was fused into short and long masses of somewhat sinuous outline ; some were completely isolated, ending in swollen bulbs, others were continued as fine black threads (Photo 2). Scattered at intervals there were many isolated finer threads and also polymorphic globules. In the middle third of the nerve these appearances were replaced by parallel sinuous rows of fine black filaments with moniliform swellings, resembling precisely the degeneration in the third nerve (Photo 3). Towards the nucleus of origin these filaments of morbid myelin became finer and fewer in number, but were easily traced curving round the ascending portion of the seventh nerve and ultimately gaining the floor of the fourth ventricle.

Seventh Nerve.—The degeneration here was less than in the third, fifth, or sixth nerves, and approximated rather to that in the fourth. Its commencement at the point where the neurilemma sheath left the fibres was easily demonstrable, and it steadily decreased centralwards ; in fact towards the nucleus there were only traces of altered myelin. The degeneration in the distal portion and ascending limb was mostly of the fragmentary type, with a few examples of filiform myelin change.

Eighth Nerve.—The degeneration was slight and only recognisable in the cochlear division in the form of a few black threads with moniliform swellings ending abruptly lateral to the restiform body.

Ninth, Tenth, and Eleventh Nerves.—The degeneration in these was so insignificant as to be negligible ; while in the *twelfth* only a few blackened myelin threads were visible amongst the nerve strands.

Rabbit 2.—Capsule under Skin of Cheek.—Third Nerve.—The degeneration was very slight. Along the course of the nerve there were flakes of altered myelin and short rows of globules ; fine black threads were rare.

Fourth Nerve.—Exactly as in the third.

Fifth Nerve: (A) Motor Portion.—Here the degeneration was of the same

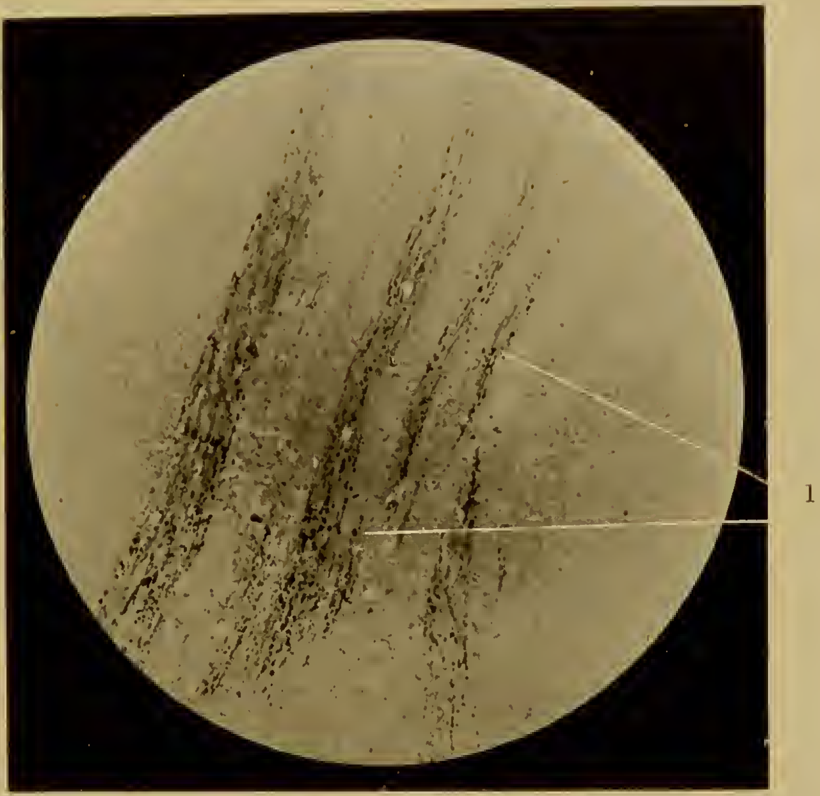

PHOTO 1.—Expt. 1. 3rd cranial nerve. Fine beaded myelin threads.

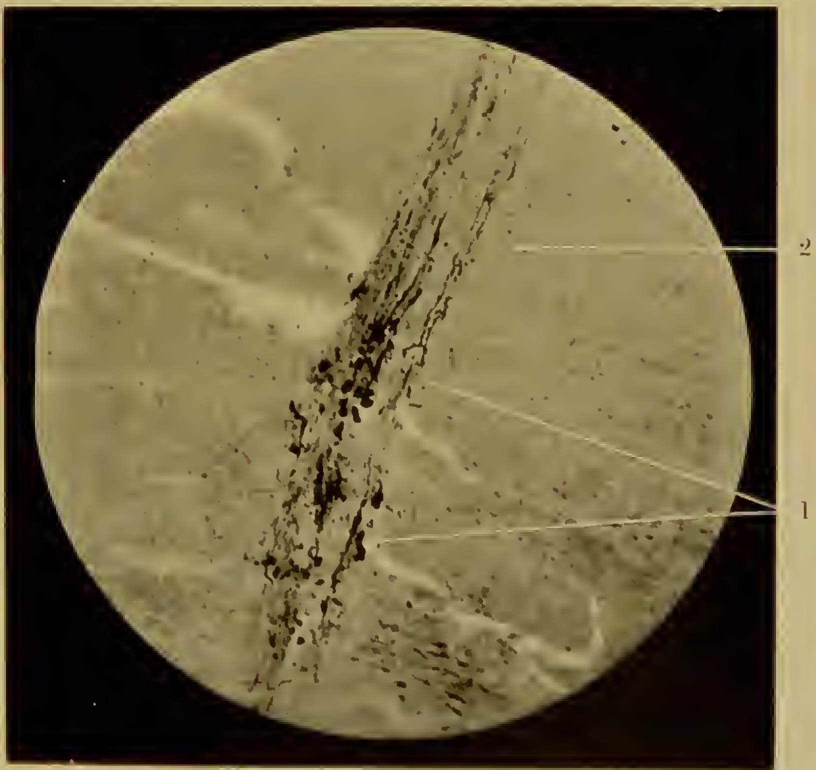

PHOTO 2.—Expt. 1. Anterior third of 6th cranial nerve. 1. Distal portion showing swollen globules of degenerated myelin. 2. More central portion showing black myelin threads.

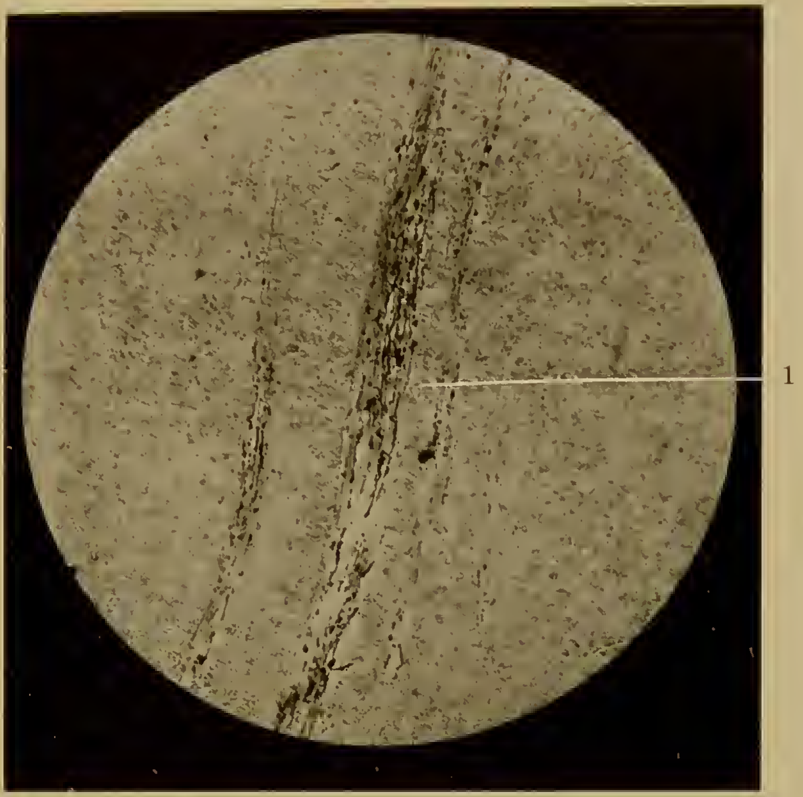

PHOTO 3.—Expt. 1. Middle third of 6th cranial nerve. 1. Sinuous rows of fine black filaments with moniliform swellings.

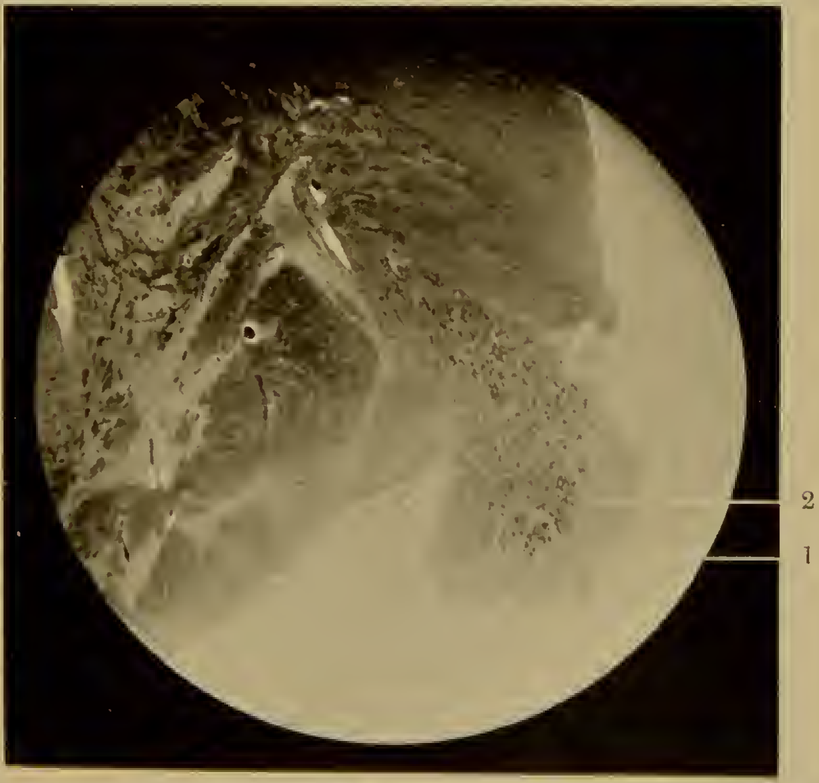

PHOTO 4.—Case 1. General Paralysis. 5th cranial nerve. 1. Extra-medullary portion normal. 2. Degeneration commencing at the point where neurilemma is lost (intra-medullary).

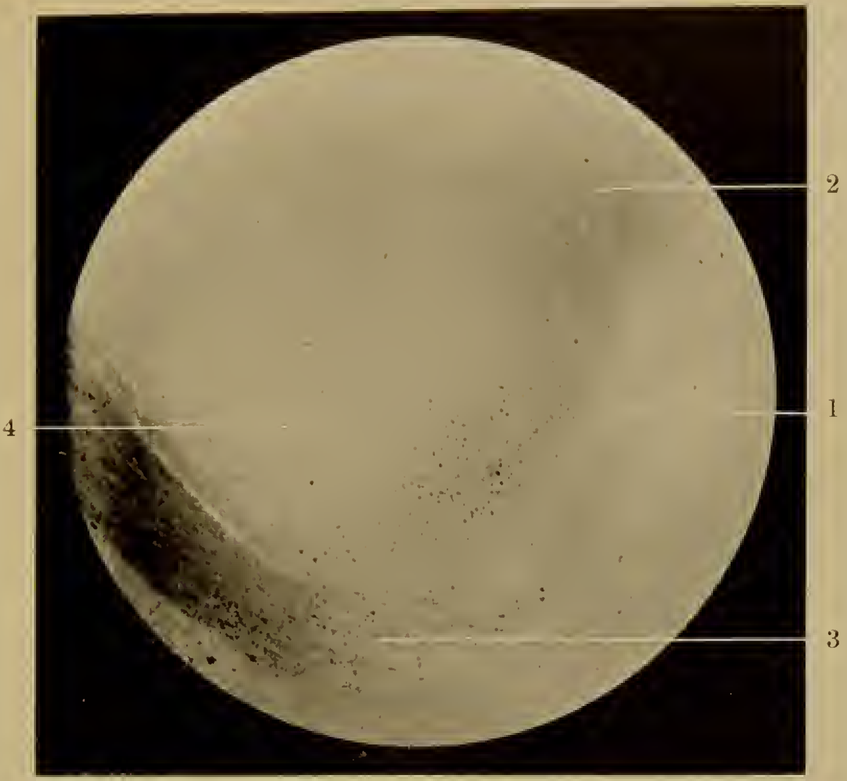

Photo 5.—Expt. 2. 1. Ascending root of 5th cranial nerve, containing many degenerated fibres cut in transverse section. 2. 8th nerve. 3. 7th nerve. 4. 5th nucleus.

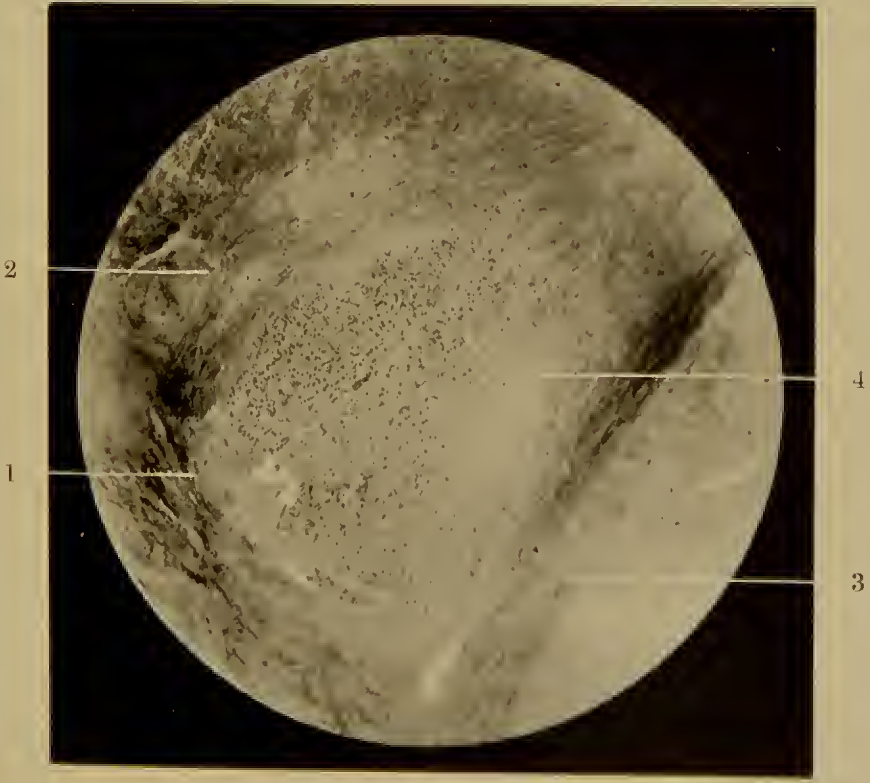

Photo 6.—Case 1. General Paralysis. 1. Descending root of 5th cranial nerve, containing many degenerated fibres cut in transverse section. 2. 8th nerve. 3. 7th nerve. 4. 5th nucleus.

type as in the third nerve, but a little more marked. It commenced as soon as the fibres lost the neurilemma and could be traced into the main nucleus of origin, and for a short distance up the mesencephalic root. (*B*) *Sensory Portion.*—The degeneration in this root was very intense, especially at and immediately inside the point where the fibres lost the neurilemma sheath. The altered myelin globules, some small, some large, lay end to end in rows. Frequently one met as many as ten small globules so arranged, and occasionally also fine myelin threads with moniliform swellings in parts disintegrating into fine black granules. In appearance the degeneration coincided with that termed Wallerian, and was traced in the descending root as far as the lower part of the medulla (Photo 5).

Sixth Nerve.—There was more degeneration here than in the third and fourth nerves, and it attained its maximum in the anterior third just inside the corpus trapezoides. The myelin was fused into globules of varying size and shades of osmic acid staining, some being dark brown, others black; but the blackening was never so striking, nor the myelin fusion so complete as in the preceding case. Even portions of the same globule varied in shade, and the large majority were vacuolated. Many sinuous threads were present, black or brown in colour, which often formed connecting bands between adjacent fusiform masses of degenerated myelin, or others separated by a considerable interval (Photo 7). Half way towards the nucleus these threads were still present, but absent in the posterior third of the nerve and at the nucleus itself.

Seventh Nerve.—The degeneration was slightly greater than in the third, fourth, and motor root of the fifth nerve, and was practically confined to the distal intramedullary portion, where the nerve emerges. Here the myelin had disintegrated into small and large globules arranged in rows; there were a few examples of the thread form of degeneration.

Eighth Nerve.—The degeneration was very slight, and in the other nerves, ninth, tenth, eleventh, and twelfth, there was no change worthy of note.

It is necessary to preface the description of the experiments on the cord by stating that in the first, in addition to placing a capsule under the sciatic nerve, one was implanted under the muscles covering the upper dorsal region. The wound here became septic twenty-seven days after the operation, owing to rupture of the capsule, and the pus invaded the cervical region on the right side before the accident was discovered, when the animal was immediately killed.

Rabbit 3.—In the lowest segments of the cord no degeneration was present. In the lumbar enlargement, however, the osmic acid method yielded a very definite positive reaction. The degeneration of the exogenous system commenced immediately the fibres lost their neurilemma sheath, involved the root entry zone and the whole of the posterior columns with the exception of a small area behind the commissure, and the posterior periphery of the cord. There was considerable degeneration of the collaterals, most evident in those running through the antero-internal angle of Rolando's substance into the posterior grey horns; while those passing towards the anterior cornua showed much less alteration (Photo 11). From the lumbar region upwards through the lower dorsal cord there was a steady diminution in the number of degenerated fibres, those remaining being scattered around the median septum; but in the upper dorsal region degeneration again appeared in the root entry zones, especially in that of the right side. The degeneration here, however, had not the systematic character of that in the lumbar enlargement. On reaching the cervical region there was a marked increase in the number of degenerated fibres, these almost completely filling the posterior columns and leaving free the same areas as noted in the lumbar cord. The collaterals leaving the root entry zones were degenerated, but not further forwards than the level of the commissure.

The Marchi reaction in this case was, in the large majority of instances, of the usual type seen in transverse section, each degenerated fibre showing as a solid black globule; but occasionally appearances indicating partial degeneration of the myelin were met with. For example, Photo 8 shows a fibre in which the black degenerated outer and periaxial portions of the myelin are separated by a clear ring in which the osmic acid reaction is negative. This middle area in many other examples stained dark grey or brown, the colour gradually merging into the black on either side. Occasionally, too, the peripheral part of the myelin alone stained. In the root entry zones sometimes there were solid, elongated segments of degenerated myelin (Photo 9). In longitudinal section the degeneration showed as long parallel lines of myelin droplets.

Rabbit 4.—The description of the degeneration in the above experiment holds good for this one with this exception, that here the morbid changes were not so advanced; so that partial degeneration was very frequently seen (Photo 8). The degeneration diminished rapidly on passing from the lumbar to the dorsal region.

Rabbit 5.—Of the three cords this was least affected. The distribution of the lesion in the lumbar enlargement was the same, but the affection of the collaterals was much less noticeable. There were many more examples of partial degeneration, sometimes only three-fourths of the myelin circumference being blackened, leaving the remaining fourth merely darkened. There were many fibres in which the myelin was degenerated only round the axis-cylinder, the outer myelin ring remaining normal; in others this also was blackened, leaving a middle clear zone. The uniform degeneration of the whole diameter of the fibre was not found nearly so frequently as in the other two cords.

The extra-medullary part of the posterior roots and of the cranial nerves was examined by Marchi's method. No degenerative changes were found. In the cord of one case (Experiment 3) there was some degeneration of the lateral columns in the vicinity of the posterior horns in addition to that already noted in the posterior columns; but in the pons (Experiments 1 and 2) the degeneration kept strictly to the course of the nerves with one exception, viz. in Experiment 1, in which there was some degeneration of the fibres of the corpus trapezoides for a short distance on either side of the sixth nerve.

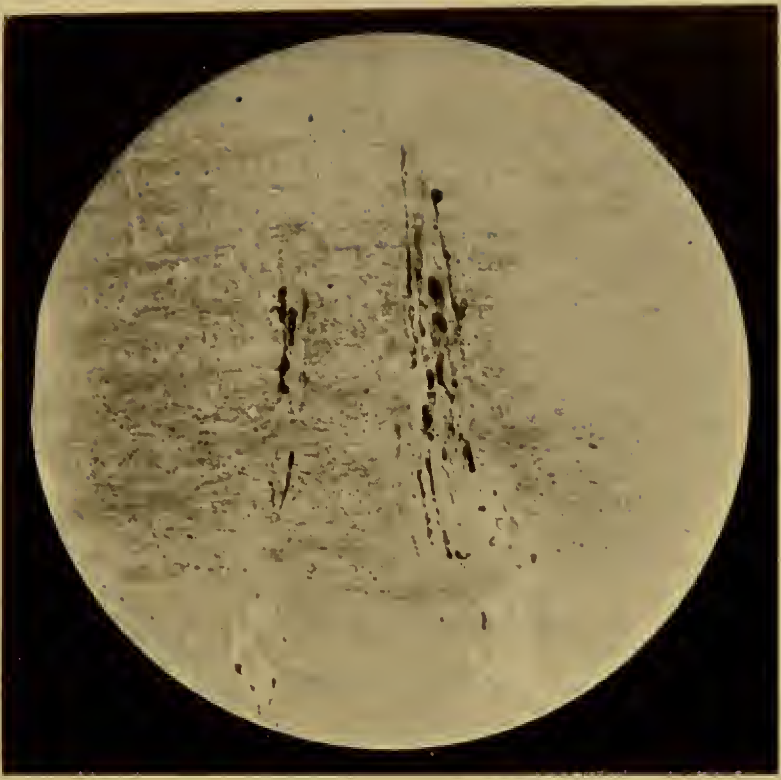

PHOTO 7.—Expt. 2. 6th cranial nerve.

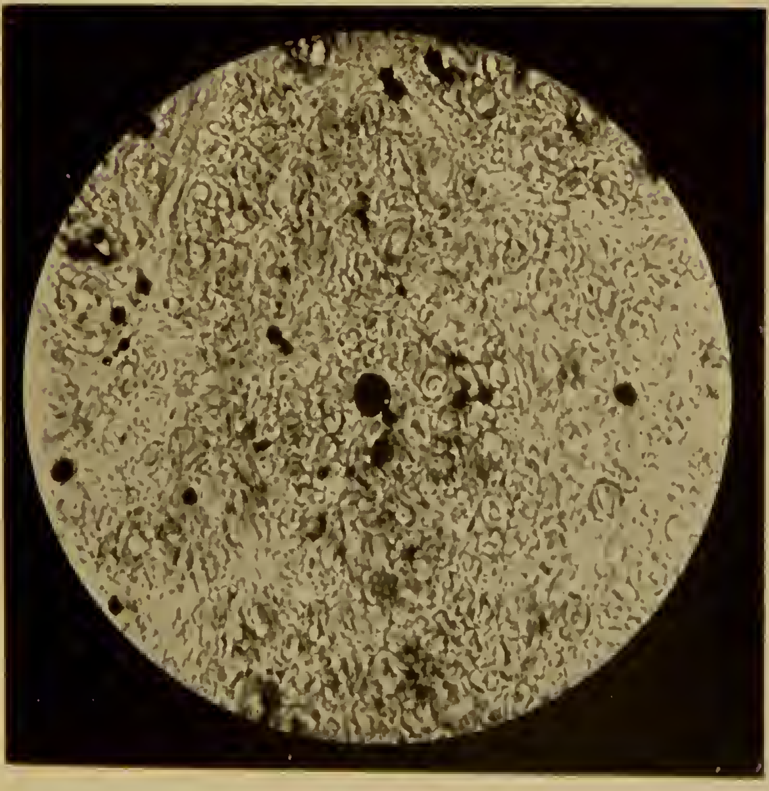

PHOTO 8.—Expt. 3. Degeneration of inner and outer parts of fibre.

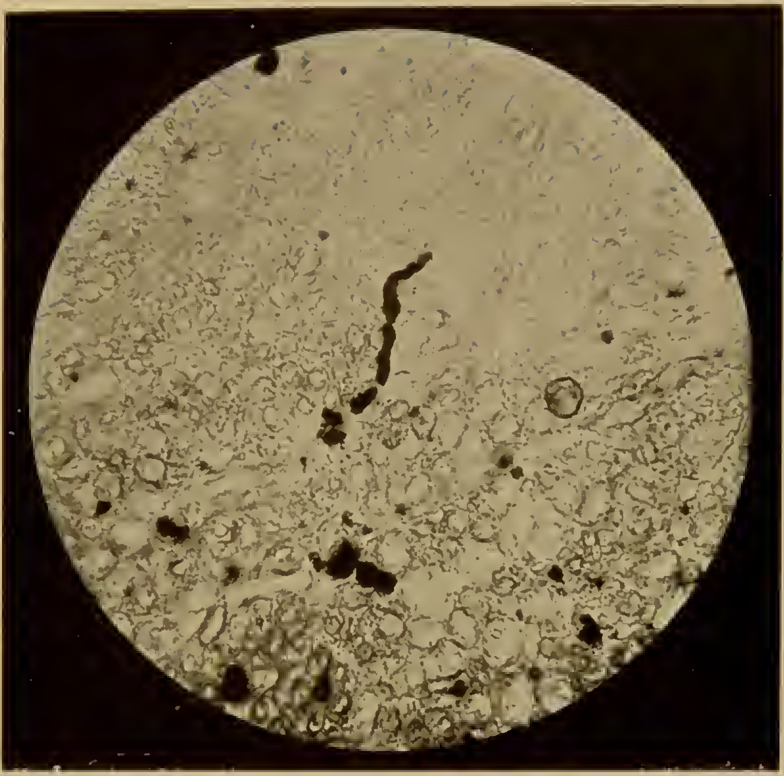

PHOTO 9.—Expl. 3. Elongated segment of degenerated myelin.

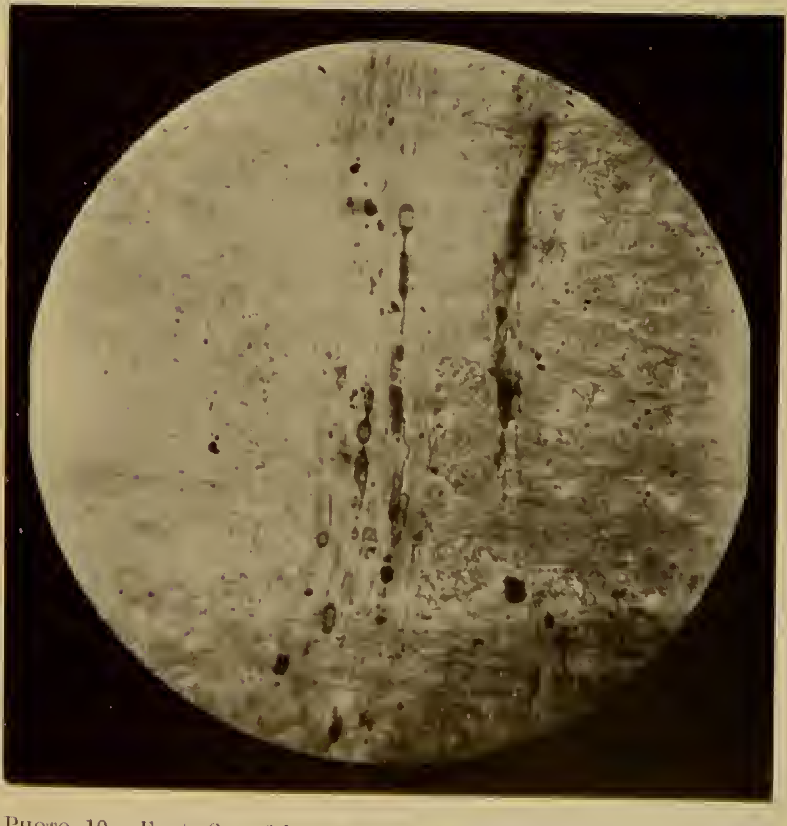

PHOTO 10.—Expt. 2. 6th cranial nerve; darkening of myelin sheath with vacuolation.

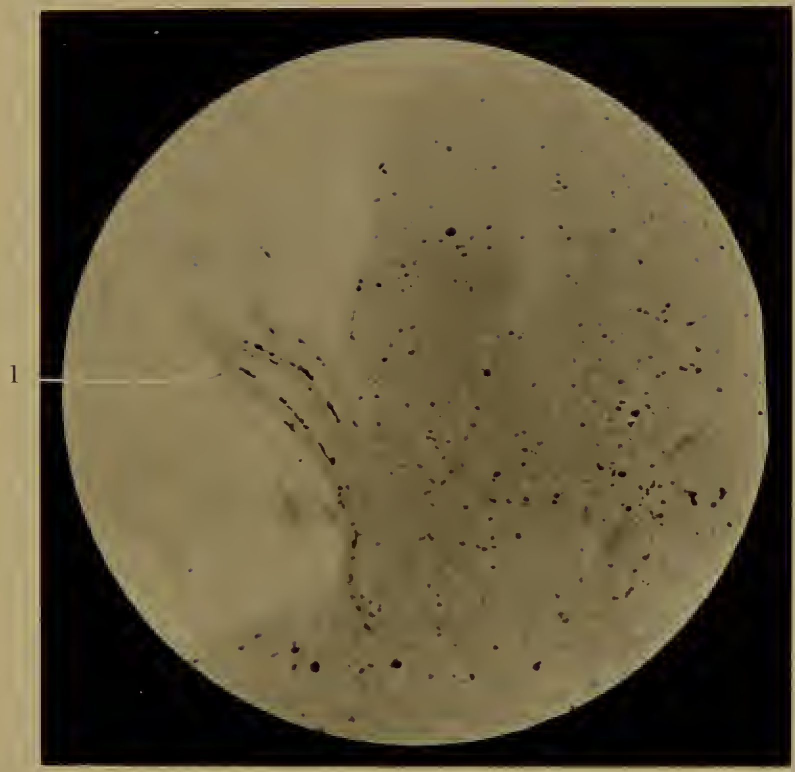

Photo 11.—Expt. 3. Degeneration of posterior columns and of the collaterals passing into the posterior grey horn.

In discussing the nature of the degenerations above described it will be advantageous to commence with a motor cranial nerve. Taking the sixth as an example, and comparing the lesions in Experiments 1 and 2, we can follow the degeneration from an early to an advanced stage. The initial change (Experiment 2) is a darkening of the myelin sheath with swelling and vacuolation (Photo 10), passing on to the formation of the thick fusiform masses and thin, elongated, moniliform structures which characterise the later degeneration in Experiment 1. The distal part of the intramedullary portion of the nerve suffers first (Experiment 2), followed by involvement of its whole length back as far as the nucleus of origin (Experiment 1). Meanwhile the extramedullary portion remains intact. The lesion, therefore, is not Wallerian, such as was present in the fifth descending root (Experiment 2), for, commencing distally, it extended centralwards and gradually diminished in that direction as the toxin lost potency in its progress along the nerve. Both in appearance and in its mode of extension this degeneration is typical of that found in toxic conditions, and strongly resembles in character the variety known as "segmentary necrosis."[1] The black fusiform masses and long sinuous threads point clearly to an acute necrotic or liquefactive change in the medullary sheath. As to whether the axis-cylinder was involved in the process we cannot say without supplementing the Marchi method by other stains.

In the other cranial nerves and in the cord there is abundant additional evidence of primary myelin degeneration of varying degree, well exemplified in the transverse sections of the cord. All stages of alteration are present, from that confined either to the neighbourhood of the axis-cylinder or to the periphery of the myelin ring (Photo 8), to a more advanced phase where the medullated sheath is seen as a solid black globule. Where these globules are present in sufficient number and can be traced in a centrifugal direction for some distance, one must admit involvement of the axis-cylinder with Wallerian degeneration, *e.g.* in the fifth descending root of Experiment 2 and of Case 1, and in the root entry zones and collaterals of the cord in Experiment 3. In toxic conditions, therefore, primary myelin change is the forerunner of secondary degeneration whose onset must be determined either by the intensity of the toxin or by the duration of its action. Low virulence will account for the slow myelin atrophy and disintegration so often met with in many nervous affections, and we need only mention in this connection general paralysis and tabes dorsalis, in which much myelin degeneration can exist with comparative integrity of the axis-cylinders. But there comes a time when this structure's resistance is overcome in the natural course of events or by a rise in virulence of the exciting toxin, and secondary degeneration ensues. In general paralysis of the acutely delirious type we have seen acute Wallerian degeneration in the posterior columns of the cord and in the cranial nerves, which could only be produced by some very potent toxin ; while in other chronic cases there have been changes ranging from simple atrophy to more advanced phases of degeneration. It is this variation in toxicity which constitutes the difference between the slow and rapid types of the above mentioned progressive lesions.

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[1] Cornil et Ranvier. Man. D'Histol. Pathol., T. 3, pp. 688, 715.

CONCLUSIONS.

(1) In peripheral nerves, spinal roots, and cranial nerves there is a constant stream of lymph ascending towards the central nervous system whose main current lies in the inner meshes or lymph spaces of the fibrous perineural sheath. Toxins reach the spinal cord and brain by this channel ; and although they spread to some extent in the lymph spaces of the pia-arachnoid, and so affect structures at a distance from their point of entry, for the most part they pass, in the main current of the lymph, along the nerve roots into the substance of the central nervous system. Here they apparently follow the nerve paths of the affected roots, and show little tendency to diffuse amongst the neighbouring fibres (Photos 2 and 3). (2) In their extramedullary portion these nerves are protected from the influence of the toxins by the vital action of the neurilemma sheath, but on losing this in their intramedullary part they at once undergo degeneration. (3) The first change is a primary degeneration of the myelin ; the axis-cylinders and nerve cells are evidently affected later.

Since writing the above, we have met with and are now investigating a case of general paralysis which bears out to a very marked degree the experimental and clinical evidence given above. At the autopsy the following morbid appearances were found, suggesting the presence of some infective condition, *e.g.* acute catarrh and ulceration of the large intestine with hæmorrhages, especially of its lower portion, chronic thickening of the mucous membrane of the bladder, with an acute cystitis and very offensive blood-stained urine. In addition we should mention the presence of a septic condition of the right knee-joint which had existed for two weeks previous to death. Cultures were made from the cerebro-spinal fluid of the lateral ventricles and of the lumbar region, and yielded an abundant growth of a rod-shaped bacillus which often assumed a long thread-like form. In sections of the right sciatic nerve we failed to find any organisms, but found them abundantly in the following regions, viz.: in the internal layers of the perineural sheath of the posterior and anterior lumbar roots, amongst the fibres of the posterior root entry zone, in the pia-arachnoid around both sides of the cord, and in the septa passing into the cord where they were most numerous at the periphery, amongst the anterior root fibres, and a few in the central canal and surrounding tissues. In the spinal roots the organisms also followed the track of the vessels passing into the centre of the nerves. In both roots and cord there were many in the adventitial lymph spaces of the vessels, but nowhere did we observe a single organism within the lumen. The vessels were dilated, and there was cellular infiltration of their walls. In the cord the organisms were found to be limited to those areas which we have shown to be affected as a result of toxic absorption (8). This is especially well illustrated in comparison with a case of brachial neuritis (10). It will be seen here that the distribution of the myelin degeneration in the posterior root entry zone, the anterior radicular zone, around the pia-arachnoid, and along the septa to the central parts of the white matter, coincides exactly with that of the organisms in the present case.

The presence of the organisms in the adventitial sheath of the vessels and their entire absence within the lumen are facts of very great significance. We would suggest that this infection of the adventitia is secondary to the infection of the lymph circulating amongst the nerve fibres. In support of this view we would mention that it is frequently found, in advanced phases of cord degeneration, that the fatty products in process of granular disintegration and absorption pass into the adventitia and fill the cells and spaces there until the vessel wall may be stained almost uniformly black with osmic acid. It is possible that this is the true explanation of the vascular changes found in the cord in acute myelitic lesions, and that these should not be considered as being of primary hæmatogenous origin, but as being reactive changes due to a primary lymphogenous infection of the adventitia of the vessel walls.

REFERENCES.

1. Orr and Rows. *Brain*, Winter, 1904.
2. Levi. *Arbeit. a. d. neur. Instit. a. d. Wien. Universität*, Bd. 13, 1906.
3. Marie et Morax. Quoted in Cornil et Ranvier, Man. D'Hist. Pathol., T. 3, p. 721, 1907.
4. Homén and Laitinen. See Homén, *Arbeit. a. d. path. Instit. zu Helsingfors* (Finland), 1902.
5. Pirrone. *Rif. Med.*, 1905.
6. Guillain. Cornil et Ranvier, T. 3, p. 719.
7. Sicard and Bauer. Cornil and Ranvier, T. 3, p. 719.
8. Orr and Rows. *Rev. Neurol. and Psych.*, Jan. 1906.
9. Medea. *Riv. Speriment. di Fren.* Fasc., 1 and 2, 3 and 4, 1906.
10. Orr. *Rev. Neurol. and Psych.*, October 1903.